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Review

Complications of Herpes Zoster

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Abstract

Background: Most clinicians easily diagnose typical clinical signs and symptoms of herpes zoster. However, in certain circumstances and in special populations, herpes zoster can present with rare manifestations and can cause potentially life-threatening complications. Clinicians must be aware of these presentations and be prepared to perform appropriate diagnostic studies. Clinical importance of herpes zoster arises from mainly its complications. Quick identification of these complications and proper early management are essential to decrease their severity and improve outcomes.

Herpes zoster, or shingles, is a self-limiting, dermatomally localized painful blistering rash caused by reactivation of varicella zoster virus (VZV), the causative agent of chickenpox [1]. VZV is a ubiquitous, double-stranded DNA virus which belongs to the subfamily of human alpha herpes virus [2]. In the course of herpes zoster, there is usually no fever or other systemic symptoms [3]. Clinical importance of herpes zoster arises from mainly its complications, especially pain. Quick identification of these complications and proper early management are essential to decrease their severity and improve outcomes [4]. In this review we aimed to focus on herpes zoster complications in a detailed manner. Complications of herpes zoster can be classified into four categories according to affected system; cutaneous, ocular, neurological and visceral [1,3]. Complications also develop acute, chronic or both. Complications affecting skin, eye, and nervous system are rather common, whereas complications in visceral organs are relatively rare (**Table 1**).

Neurologic and Ocular Complications

Herpes Zoster and Pain

Pain is the most annoying symptom of herpes zoster. It often precedes and generally accompanies the rash. But, approximately 20% of patients will continue to experience pain persisting 4 weeks after rash healing, a condition known as postherpetic neuralgia (PHN) [5]. PHN occurs with sufficient frequency that it should be considered a part of the natural component of the disease. For pain classification, two methods are preferred. The easiest approach is to term all pain developing immediately, preceding or after zoster as "zoster-associated pain" (ZAP). Another classification system separates acute pain (within the first 30 days), subacute pain (between 30 and 120 days), and chronic pain (lasting >120 days) [6].

Two different but overlapping mechanisms appear to be involved in the pathogenesis of ZAP: sensitization and deafferentation [7]. Sensory nerves that mediating pain (nociceptors) become sensitized following injury, re-

Table 1. Complications of Herpes Zoster

	Cutaneous and Mucocutaneous Sites	Neurological	Ocular	Visceral
Acute complications	Cutaneous VZV dissemination Bacterial superinfection Cellulitis Zoster gangrenosum Zoster haemorrhagicus Septicemia	Meningo-encephalitis Aseptic meningitis Granulomatous arteritis Segmental pareses Cranial nerve palsies Peripheral nerve palsies	Conjunctivitis Episcleritis/scleritis Uveitis Keratitis Iridocyclitis Secondary glaucoma Acute retinal necrosis Loss of corneal sensation Optic neuropathy Ptosis Mydriasis	Neural extension of VZV infection Bronchitis, Pleuritis Esophagitis Gastritis, Enterocolitis Peritonitis Cystitis Myositis Pericarditis Visceral VZV dissemination Pneumonia Hepatitis, Pancreatitis Myocarditis, Arthritis
Chronic complications	Persisting zoster Scar formation (atrophic scars, hypertrophic scars) Hypo/depigmentation Granulomatous skin lesions Pseudolymphoma Manifestation of psoriasis (*Köbner*'s phenomenon)	Post-herpetic neuralgia *Guillain-Barre´* syndrome Transverse myelitis Ascending myelitis Motor neuropathy Autonomic dysfunction Granulomatous cerebral angiitis Diaphragmatic paralysis Bladder dysfunction Sensory loss Deafness Cicatricial lid scarring Vestibular dysfunction Abdominal hernias	Keratitis Chorioretinitis Retrobulbar neuritis Vasculitis Panophthalmitis Atrophy of optic nerve Progressive outer retinal necrosis	

sulting in continuous discharge and peripheral sensitization (hyperexcitability). Prolonged discharge of the nociceptor enhances the dorsal horn neurons to afferent stimuli and expands the dorsal horn neuron's receptive field (central sensitization), leading to allodynia and hyperalgesia [**8**]. Allodynia, is a pain due to a stimulus which does not normally provoke pain such as light touch. Hyperalgesia is an extremely painful reaction to a stimulus which is normally producing mild pain. In addition, neural destruction causes spontaneous activity in deafferented central neurons, generating constant pain. The spinal terminals of mechanoreceptors may contact receptors formerly occupied by C-fibers, leading to hyperalgesia and allodynia [**9**]. The loss of function or death of dorsal horn neurons, which have an inhibitory effect on adjacent neurons, contributes to an increase in activity being transmitted up the spinal cord. The central sensitization is initially temporary (self-limited), but may become permanent. According to its quality, three basic pain types have been described: 1- constant, monotonous, usually burning or deep, aching pain; 2- the shooting, lancinating (neuritic) pain; and 3- triggered pain (allodynia or hyperalgesia) [**7,10**]. Age is the most significant risk factor for development and persistence of PHN. Other risk factors for PHN include the presence of prodromal pain, severe pain during the acute phase of herpes zoster, greater rash severity, more extensive sensory abnormalities in the affected dermatome and, possibly, ophthalmic (as opposed to thoracic or abdominal) herpes zoster [**5,11**]. Postherpetic neuralgia affects up to 34% of those with zoster in the general population, but about 60% to 70% of patients age 60 years and older who develop zoster [**9**]. In some patients skin rash may develop without any significant pain. Conversely, there may be strong unilateral pain without cutaneous lesions. This situa-

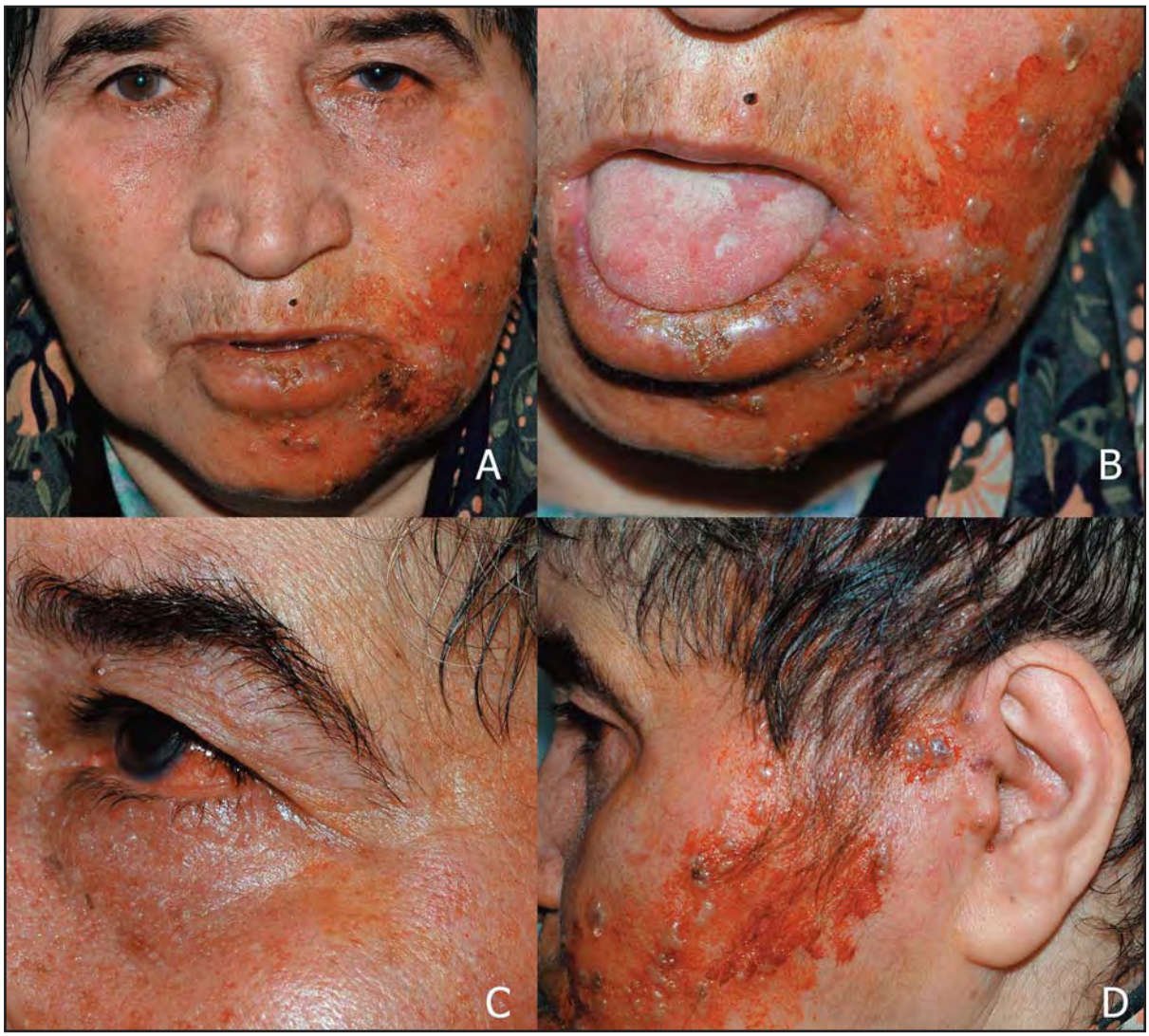

Figure 1. Unilateral distribution herpes zoster involving the mandibular branch of the fifth (trigeminal) nerve; a few vesicles cross the midline at chin (A). Tongue (B), conjunctiva (C) and earlobe (D) involvement. (Red color at the skin background is due to rifampicin application)

tion is named as zoster sine herpete [**12,13**]. Pruritus, paresthesia, dysesthesia and anesthesia are other abnormal sensations which can persist after healing of skin lesions [**14, 15**]. Management of PHN is not easy and vaccination for prevention of PHN may be the choice of future [**16**].

Long list of rare and atypical complications are encountered especially in high-risk populations. Immunosuppression is the major risk in this group and it increases the morbidity and mortality associated with herpes zoster. It may be associated with malignancy (especially hematological), HIV infection or medications used for organ transplantation or autoimmune disease (corticosteroids, chemotherapeutic agents, cyclosporin and tacrolimus) [**17**].

Development of herpes zoster at cranial region has special importance. Involvement of cranial nerves has high complication risk. Fifth cranial nerve (trigeminal nerve) has three branches; ophthalmic, maxillary, mandibular. In ophthalmic zoster the eye is affected in two-thirds of cases, especially when vesicles on the side of the nose indicate involvement of the nasociliary nerve (*Hutchinson*'s sign) [**18**]. *Hutchinson*'s sign is a powerful predictor of ocular inflammation and corneal denervation. Also vesicles on the lid margin are virtually always associated with ocular involvement. Ocular complications include uveitis, keratitis, conjunctivitis, conjunctival edema (chemosis), ocular muscle palsies, paralytic ptosis, proptosis, scleritis (which may be acute or delayed for 2–3 months), retinal

vascular occlusion, acute retinal necrosis and ulceration, scarring and even necrosis of the lid. Involvement of the ciliary ganglia may give rise to *Argyll–Robertson* pupil [**18, 19**]. Anterior uveitis and the various varieties of keratitis are most common, affecting 92% and 52% of patients with ocular involvement, respectively. Sight threatening complications include neuropathic keratitis, perforation, secondary glaucoma, posterior scleritis/orbital apex syndrome, optic neuritis, and acute retinal necrosis [**6, 20**]. Ophthalmic nerve sends branches to the tentorium and to the third and sixth cranial nerves, which may explain the meningeal signs and, occasionally, the third and sixth cranial palsies associated with herpes zoster ophthalmicus [**17, 18**]. When the maxillary and mandibular branches of the trigeminal nerve are involved oral herpes zoster may develop that involving the hard palate, uvula, tonsillar area and maxilla (second branch) or anterior part of the tongue, the floor of the mouth, the buccal mucous membrane and mandible (third branch) (**Figure 1**). In orofacial zoster, toothache may be the presenting symptom sometimes without mucosal lesions [**12, 19**].

The facial nerve (seventh cranial nerve) is most commonly affected cranial nerve and mainly a motor nerve. When just the external ear is affected, it is named as herpes zoster oticus [**6, 21**]. Pressure on the facial nerve motor fibres may evolve into facial palsy. The vestibulocochlear nerve (eighth cranial nerve) and the facial nerve involvement complete the classical triad of the *Ramsay–Hunt* syndrome; herpes zoster of external ear or tympanic membrane, ipsilateral facial paralysis and auditory symptoms [**22, 23**]. Compression of the vestibulocochlear nerve may cause auditory symptoms which are sensorineural hearing loss, tinnitus, dizziness and vertigo. Involvement of the nervus intermedius or its geniculate ganglion would impair taste sensation from the anterior two-thirds of the tongue and alter lacrimation [**19, 24**]. Herpes zoster oticus accounts for about 10% of cases of facial palsy. The paralysis is usually complete and full recovery occurs in only about 20% of untreated cases. There is permanent hearing loss in about one-third of these patients. Maxillary and mandibular alveolar bone necrosis and limited or widespread loss of teeth may result [**6, 19**].

Meningoencephalitis and myelitis have been reported in 0.2% to 0.5% of patients and are associated with headache, fever, photophobia, meningeal irritation, vomiting, nerve palsies, or altered mental state. Neurologic symptoms usually start within the first 2 weeks of onset of the skin lesions. It is believed that encephalitis is immune mediated rather than a consequence of viral invasion [**24, 25**]. Patients at highest risk are those with trigeminal and disseminated zoster, as well as the immunosuppressed. The mortality rate is high (10% to 20%); but most survivors recover completely. To verify the diagnosis is very hard due to the fact that the virus is rarely isolated from the spinal fluid. Cell counts and protein concentration of the spinal fluid are elevated in encephalitis and in approximately 40% of typical zoster patients [**24, 26**].

Chronic VZV encephalitis is seen almost exclusively in patients with AIDS or other conditions with depressed cellular immunity. Diagnosis is difficult, since the encephalitis may develop months after an episode of herpes zoster. Multifocal white matter lesions with small vessel vasculitis and demyelination are seen in pathology. The clinical findings are usually subacute with headache, fever, mental status changes, seizures, and focal neurologic defects, including aphasia, hemiplegia, and visual field cuts. Magnetic resonance imaging studies and examination of CSF reveal diagnostic clues. The clinical course is usually progressive deterioration and death [**24, 27**].

Delayed contralateral hemiparesis is a rare but serious complication of herpes zoster that can occur weeks to months following herpes zoster ophthalmicus. Direct VZV invasion of cerebral arteries by extension along intracranial branches of the trigeminal nerve, resulting in inflammation of the internal carotid artery or one of its branches on the side of the rash [**24**]. Headache and hemiplegia are typical presentations. CSF examination shows mononuclear cell pleocytosis and increased protein. Arteriography is usually diagnostic and demonstrates inflammation, narrowing, and thrombosis of the proximal branches of the anterior or middle cerebral artery. Antiviral therapy is advised due to presence of VZV in the inflamed arteries, but it is difficult to assess benefit of drug since irreversible cerebral infarction has often occurred by the time of diagnosis. The mortality rate is 20%-

25% and risk of permanent neurologic sequelae among survivors is high [**24, 28**].

A late CNS complication of ophthalmic zoster is granulomatous cerebral angiitis with symptoms often occur weeks to months after the attack. This has been associated with a rather high mortality rate (15%) and may present as transient ischemic attacks, stroke, or isolated or multiple cerebral infarctions. Rarely, zoster involvement of the vagus nerve or its ganglia can result in dysphagia, nausea, vomiting, gastric upset and cardiac irregularities. Motor paralysis from direct extension from the sensory ganglion to anterior horn cells occurs in 1% to 5% of patients with zoster. This paralysis usually occurs in the first 2 to 3 weeks after rash onset and can persist for several weeks. Localized motor deficiencies are found in up to 20% of patients with zoster involving the facial nerve or the nerves of the extremities [**24**]. A neurogenic bladder with urinary hesitancy or urinary retention has reportedly been associated with involvement of the sacral dermatome S2, S3, or S4. Hematuria, pyuria and erectile dysfunction may also be present [**29**]. Colonic spasm, dilation, obstipation, constipation, pseudo-obstruction, and reduced anal sphincter tone can occur in abdominal zoster with the involvement of thoracic (T6 to T12), lumbar, or sacral dermatomes [**24, 30**].

Cutaneous Complications

Usually herpes zoster unilaterally involves a single dermatome. But involvement of three dermatomes is considered normal. Although it is quite rare, two or more nerve involvement is known as zoster duplex or zoster multiplex [**3,12**]. Sometimes, a few vesicles can be found remote from the primarily affected dermatome in immunocompetent patients (17%-35%), which probably result from the path of small nerve branches or hematogenous spread of the virus [**5,6**]. Cutaneous dissemination of herpes zoster defined as more than 20 vesicles outside the area of primary or adjacent dermatomes and occurs in approximately 10% of immunocompromised persons [**6**]. It is a diagnostic dilemma to differ cutaneous dissemination from recurrent varicella [**9,26**].

The most common complication of herpes zoster is bacterial superinfection of skin lesions, caused most often by Staphylococcus aureus or Streptococcus pyogenes. Elderly, malnourished, debilitated, or immunosuppressed patients tend to have a more virulent and extensive course of disease (bullous or hemorrhagic zoster). The entire skin area of a dermatome may be lost after diffuse vesiculation. Large adherent crusts promote infection and increase the depth of involvement. Bacterial cellulitis can accentuate the necrosis and scarring (sometimes hypertrophic or keloidal). Zoster gangrenosum is necrotizing soft tissue infection following herpes zoster. In some cases, septicemia can develop [**3,8**].

The most commonly reported atypical lesions are multiple hyperkeratotic papules that follow no dermatomal pattern. These lesions may be chronic, persisting for months or years, and are sometimes associated with acyclovir-resistant strains of VZV [**24**]. A second dermatologic variant is ecthymatous VZV lesions, which present with multiple large (10-30 mm) punched-out ulcerations with a central black eschar and a peripheral rim of vesicles. Postherpetic hyperhidrosis, gustatory flushing and sweating are intersting complications that reported anecdotally [**31,32**].

After herpes zoster healed, various skin lesions may develop within the affected dermatome, perhaps analogous to the long-standing immunologic ocular and CNS reactions seen in ophthalmic zoster. Lesions usually appear within a month, and rarely, longer than 3 months after the zoster. The term “isotopic response” describes the occurrence of a new, unrelated disease that appears at the same location as a previously healed disease [**33**]. Zoster is one of the most common causes of the isotopic response. A first review on this topic along with pathogenic hypotheses was presented by Wolf et al. in 1995 [**34**]; then Tuzun et al. proposed the name “Wolf's isotopic response” [**35**]. Various hypotheses have been proposed such as viral, immunological, neurological, and vascular etiologies regarding pathogenesis of this phenomenon [**36**]. Isotopic response developed site is accepted as locus minoris resistentiae (site of least resistance) so it is vulnerable for development of secondary disease [**8,37**]. A long list of skin diseases have been reported in areas of healed zoster as *Wolf*'s isotopic response. Most frequently granulomatous skin reactions such as typical granuloma annulare, to sarcoidal reactions, or even granulomatous vas-

culitis have been reported. Less commonly reported other skin diseases includes malignant tumors (breast carcinoma, squamous cell carcinoma, basal cell carcinoma, metastasis), leukemic or lymphomatous infiltrations, dysimmune reactions (lichen planus, lichen sclerosus), infections (dermatophytosis, verrucae), comedonic-microcystic reactions (acne, milia) [**36, 38**].

Herpes zoster in pregnancy: By contrast with varicella, there is almost never vertical transmission of VZV, if herpes zoster develops in pregnancy.

Conclusion

Most clinicians easily diagnose typical clinical signs and symptoms of herpes zoster. However, in certain circumstances and in special populations, VZV infection can present with rare manifestations and can cause potentially life-threatening complications. Clinicians must be aware of these presentations and be prepared to perform appropriate diagnostic studies.

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